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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,043	04/03/2000	BERND EIKMANNS	21437	6651

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	17

DATE MAILED: 04/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/529,043	Applicant(s) EIKMANNS ET AL.	
	Examiner David J. Steadman	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-65* is/are pending in the application.

4a) Of the above claim(s) *66-69* is/are withdrawn from consideration.

5)☒ Claim(s) *64 and 65* is/are allowed.

6)☒ Claim(s) *52-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 52-65 are pending in the application.

Applicants' cancellation of claims 1-17 and 32-51 and addition of claims 52-65 in Paper No. 14, filed 01/29/02 is acknowledged.

Applicants' arguments in Paper No. 14 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Lack of Unity

1. Applicants traverse the lack of unity presented in Paper No. 6 on the grounds that the polynucleotide of SEQ ID NO:1 and the encoded polypeptide of SEQ ID NO:2 share a common technical feature and the claims of Groups I (drawn to methods of producing amino acids using a pyryvate carboxylase gene) and II (drawn to a pyruvate carboxylase gene) should be co-examined. Applicants further argue that Morris (Morris et al. Biochem Biophys Res Commun 145:390-6) does not teach the polynucleotide of SEQ ID NO:1 or methods of use thereof and instead teaches a S. cerevisiae polynucleotide encoding a pyruvate carboxylase that shares little homology with the polynucleotide of SEQ ID NO:1. Applicants' arguments are not found persuasive. It is noted that claim 52 recites "a deletion, insertion, or substitution of a nucleotide" in a polynucleotide encoding the pyruvate carboxylase of SEQ ID NO: 2. As such, the claim encompasses *any* polynucleotide encoding a pyruvate carboxylase. The polynucleotide of Morris is considered a "substantially identically-effective DNA sequence" or a "a deletion, insertion, or substitution of a nucleotide" in a polynucleotide encoding the pyruvate carboxylase of SEQ ID NO: 2 and therefore, the polynucleotide of SEQ ID NO:1 and the encoded polypeptide of SEQ ID NO:2 do not relate to a single general inventive concept under PCT Rule 13.1.

The requirement is still deemed proper and is therefore made FINAL.

Claims 66-69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 112, Second Paragraph

2. Claims 52-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claims 52 and 53 (claims 54-62 dependent therefrom) are unclear in the recitation of "deletion, insertion, or substitution of a nucleotide". It is unclear from the claims and the specification as to whether the term refers to a single nucleotide deletion, insertion, or substitution or multiple nucleotide deletions, insertions, or substitutions. It is suggested that applicants clarify the meaning of the claims. The examiner has interpreted the claims as meaning multiple nucleotide deletions, insertions, or substitutions. If the Examiner's interpretation of these claims is incorrect, Applicant should so state and clarify the record.

Claim Rejections - 35 USC § 112, First Paragraph

4. The written description rejection of claims 53-63 under 35 U.S.C. 112, first paragraph, is maintained. The rejection of claims 53 (claims 54-62 dependent therefrom) and 63 was fully explained in a previous Office action (See paragraph 14 of Paper No. 11). Applicants argue that in order to comply with the requirements of 35 U.S.C. 112, first paragraph, it is not necessary to put the public in possession of the attributes and features of all polynucleotide species within the claimed genus and further that it is not necessary to disclose the allelic variations of the polynucleotide of SEQ ID NO:1. Applicants argue that a definition of allelic variants has been provided, i.e., nucleotide deletions, insertions, or substitutions of a polynucleotide encoding a pyruvate carboxylase, that is adequately supported by the instant specification. Applicants argue that allegedly interfering US Patent 6,171,833 ('833) discloses the invention as encompassing variants of the polynucleotide of SEQ ID NO:1 of '833, including substitutions,

deletions, and additions (columns 6 and 7). Applicants argue claims 60-63 are adequately supported by the instant specification. Applicants' arguments are not found persuasive.

It is noted that none of the issued claims of '833 is drawn to an allelic variant of a polynucleotide. It is further noted that claim 53 is not so limited to allelic variants as recited in claim 52. Claim 63 is drawn to a genus of transformed cells comprising said polynucleotide wherein *any* enzyme(s) which participates in synthesis of a corresponding amino acid or *any* enzyme(s) which participates in export of a corresponding amino acid is deregulated. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the claimed genus of host cells of claim 63, the functional definition of the genus, i.e., a transformed cell with deregulated enzymes, does not provide any structural information commonly possessed by members of the genus which distinguish the host cell species within the genus from others such that one can visualize or recognize the identity of the members of the genus.

Also, claim 53 is drawn to a genus of polynucleotides that may or may not encode polypeptides with pyruvate carboxylase activity. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species that are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of

species to reflect the variation within the genus. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus that embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the claimed genus of polynucleotides of claim 53 includes species that are widely variant in function. The genus of polynucleotides of claim 53 encompasses polynucleotides encoding polypeptides with pyruvate carboxylase activity, those which lack such activity but are capable of inducing an antibody specific for the polypeptide of SEQ ID NO:2 as well as an enormous number of polypeptides with neither of these functions, but possibly other undisclosed functions. As such, neither the description of the structure and function of SEQ ID NO:1 nor the disclosure of solely structural features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus.

The specification discloses only a single species of the claimed genus of polynucleotides (i.e., the polynucleotide of SEQ ID NO:1) and two species of the genus of host cells, i.e., C. glutamicum strains DM 368-3 and DG 52-5, which are insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus of polynucleotides. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

5. The enablement rejection of claims 53-63 under 35 U.S.C. 112, first paragraph, is maintained. The rejection of claims 53 (claims 54-62 dependent therefrom) and 63 was fully explained in a previous Office action. Applicants argue that a definition of allelic variants has been provided, i.e., nucleotide deletions, insertions, or substitutions of a polynucleotide encoding a pyruvate carboxylase, that would enable a skilled artisan to make and use the claimed polynucleotides. Applicants argue that point mutations are well-known in the art and even if the allele variation encodes a protein with substantial loss of enzymatic activity, the polynucleotide can be used as a probe. Applicants argue that a skilled artisan

could make and use the claimed polynucleotides without undue experimentation. Applicants argue that allegedly interfering US Patent 6,171,833 ('833) discloses the invention as encompassing variants of the polynucleotide of SEQ ID NO:1 of '833, including substitutions, deletions, and additions (columns 6 and 7). Applicants argue that even polynucleotides encoding allelic variants of pyruvate carboxylase without pyruvate carboxylase activity would be useful as probes as disclosed in '833. Applicants also argue the transformed cells of claims 60-63 are fully enabled. Applicants' argument is not found persuasive.

It is noted that none of the issued claims of '833 is drawn to an allelic variant of a polynucleotide. It is further noted that claim 53 is not so limited to allelic variants as recited in claim 52. The examiner agrees with applicants' assertion that hosts and methods of transformation are well known in the art. However, claims 53 (claims 54-62 dependent therefrom) and 63 are not enabling such that one of skill in the art could make and use the claimed polynucleotides and host cells as broadly encompassed by the claims. The specification, while being enabling for the polynucleotide of SEQ ID NO:1, vectors and host cells transformed with said polynucleotide, does not reasonably provide enablement for *all* polyncleotides with a nucleotide deletion, insertion, or substitution encoding a polypeptide with or without pyruvate carboxylase activity or *all* transformed cell comprising said polynucleotide wherein *any* enzyme which participates in synthesis of a corresponding amino acid or *any* enzyme which participates in export of a corresponding amino acid is deregulated. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). The amount of experimentation necessary to make and use all claimed polynucleotides or transformed cells with deregulated enzymes would result in undue experimentation. It is not routine in the art to screen for multiple substitutions and modifications of a polynucleotide or host cell, as encompassed by the instant claims, and the positions within an encoding polynucleotide's sequence where modifications can be made with a reasonable expectation of success in

obtaining a polypeptide with the desired activity/utility are limited and the result of such modifications is unpredictable. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the specification. Also, polynucleotide variants of SEQ ID NO:1 that encode polypeptides without pyruvate carboxylase activity will not necessarily be useful and, in fact, the vast majority of such homologues will not be useful. While applicants have demonstrated how to make and use the polynucleotide of SEQ ID NO: 1 and C. glutamicum strains DG-52-5 and DM 368-3 transformed with said polynucleotide, applicants have not taught how to make and use all polynucleotides and transformed cells as broadly encompassed by the claims. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

6. Claims 53 and 57-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Morris (previously cited on page 3 of Paper No. 11; Biochem Biophys Res Comm 145:390-396, 1987). Claim 53 is drawn to a pyruvate carboxylase gene having the sequence of nucleotides 165-3587 of SEQ ID NO:1 with a deletion, insertion, or substitution. Claims 57 and 58 are drawn to the pyc gene of claim 53 with a regulatory sequence (claim 57) or a promoter and regulatory sequence (claim 58). Claims 59-61 are drawn to a vector comprising the pyc gene of claim 53 or host cells comprising said vector or the pyc gene of claim 53. Morris teaches the polynucleotide sequence encoding *Saccharomyces cerevisiae* pyruvate carboxylase including two polyadenylation sequences (page 394). Morris teaches the polynucleotide is cloned into yeast/E. coli shuttle vector Yep24 and cloning vectors pUC19, M13mp18 and m19 (page 391). This anticipates claims 53 and 57-61 as written.

Conclusion

7. Claims 64 and 65 are in condition for allowance.

8. Claims 52-63 are rejected.

9. The requested interference against US Patent 6,173,833 has been held in abeyance until all pending claims have been deemed allowable.

Applicants' addition of claims 52-63 necessitated the new ground(s) of rejection presented in this office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 2:00 pm and from 3:30 pm to 5:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

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